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SLEEP

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Cover art: Emiliano Ponzi

It was probably not long after humans first questioned the meaning of life that someone turned to the significance of sleep. Why do we need it? Why do we spend so much of our life doing it? And what is this strange alternative reality we experience while we sleep?

These big questions still loom large, but researchers have been focusing on more practical matters. We now know how an intricate interaction of neurotransmitters in different parts of the brain switches us from being fully alert to unconscious, and back again (page S2). But the brain does not shut down — studies of its electrical activity are revealing how sleep boosts learning, providing tantalizing clues to the formation of memory (S4).

Sleep is proving important for more than the mind. Studies that restrict the duration and quality of sleep show that lost sleep can lead to metabolic disorders, immune dysfunctions and chronic disease (S6). And researchers are probing the link between sleep disruption and weight gain (S8).

At the root of many sleep problems is the way modern life — especially the advent of artificial light — has decoupled humans from the natural world, disrupting the brain's master clock (S13). Projects are underway to track this desynchronization and reveal how people differ in their tendency to sleep (S10). A lack of sleep can have pernicious effects in those with a mood disorder, and understanding why should help them manage these conditions (S14).

We also need safer ways to treat insomnia. One promising approach is to combine drugs with cognitive therapy (S16). Such sleep disturbances may be one of the first signs of neurodegenerative diseases (S19) — but could a prolonged lack of sleep cause these debilitating diseases in the first place?

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Tony Scully
Science Editor, Nature Outlook

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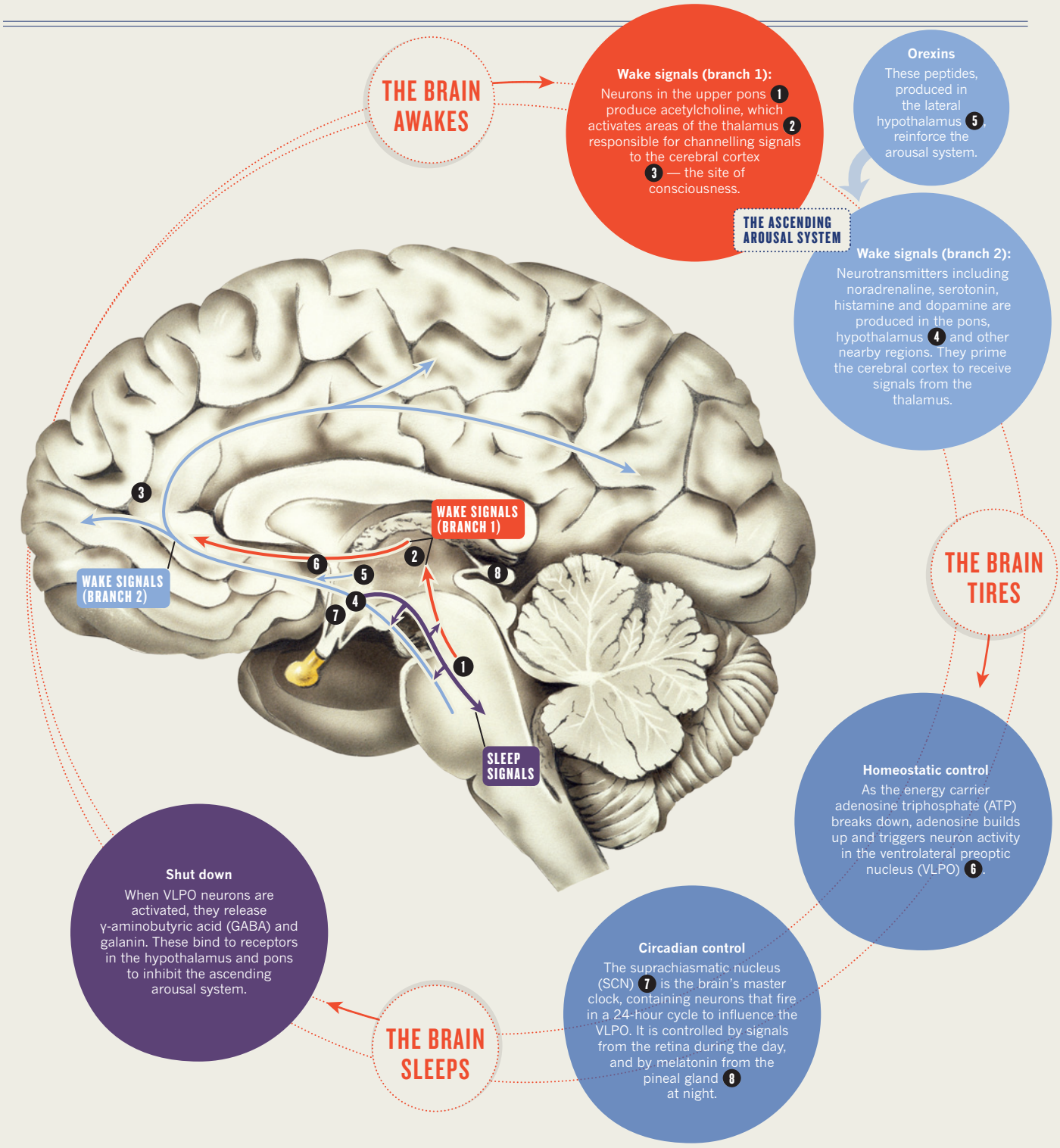
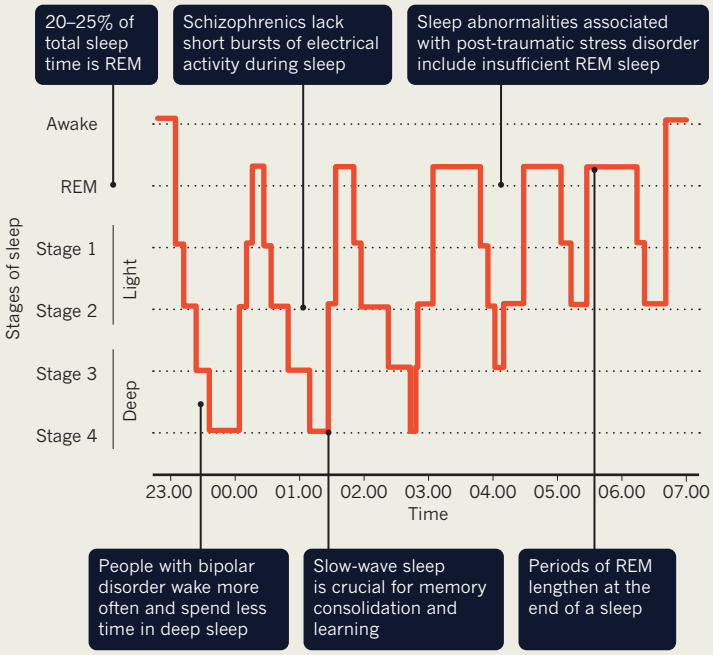
THE ANATOMY OF SLEEP

The ebb and flow of neurotransmitters switches our brains between sleep and wakefulness in carefully regulated cycles. By **Mark Peplow**.



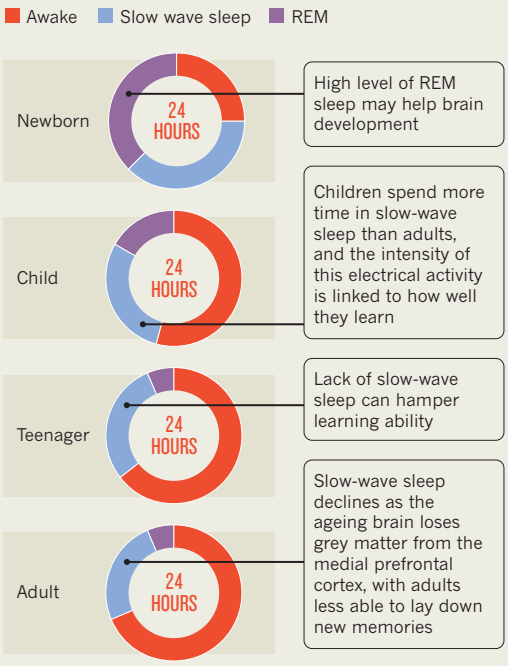
THE PHASES OF SLEEP

In a typical eight-hour sleep, the brain moves through different stages of electrical activity in repeating cycles that last about 90 minutes. Rapid eye movement (REM) sleep is linked to distinctive electrical activity in the brain, and is often associated with dreaming.



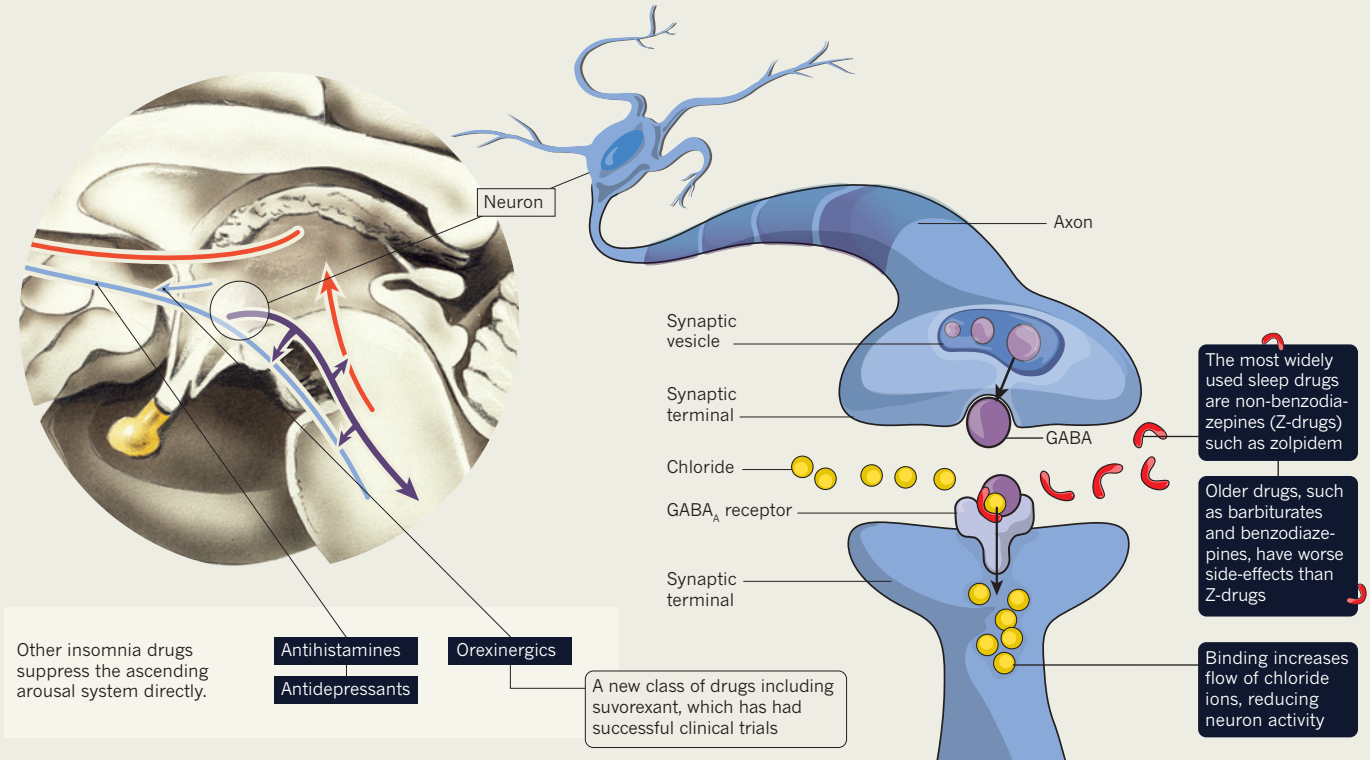
THE DECLINE OF SLEEP

After a childhood filled with blissful slumber, adulthood brings a decline in the quality and quantity of sleep.



THE DRUGS OF SLEEP

The most widely used insomnia drugs promote sleep by improving the binding of γ-aminobutyric acid (GABA) to chloride ions released by the ventrolateral preoptic nucleus (VLPO) to suppress the ascending arousal system.



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NEUROSCIENCE

Off to night school

One of sleep's most important functions is processing memory. Researchers are now starting to figure out how the brain helps us learn when we're asleep.

BY KERRI SMITH

Neuroscientist Jan Born is quietly jealous of his eight-month-old daughter. "She sleeps when she wants," he says. Then again, he says, sleep is a crucial time for learning, and she probably has more to learn about the world than the average adult. "I think about whether she needs this sleep because her hippocampus is full," he says.

The hippocampus is a node in the brain's memory network, the place memories are first encoded for transferral later to longer-term storage. Sleep is one way its contents are downloaded to other regions of the brain where it is thought they are interpreted and stored. "We know that during sleep the brain processes a wide range of memory types," says Robert Stickgold, a neuroscientist at Beth Israel Deaconess Medical Centre in Boston, Massachusetts.

Researchers know that a bit of shut-eye helps you recall all manner of things, from newly acquired motor skills, such as how to play the piano, to what you wore to the theatre last night.

But sleep is not a passive storage process, like saving a video file to a hard drive. Sleep also reconfigures memory. It helps us edit the files — adding or removing content or emotional tone, for example — and re-save them. "This isn't just memory representation getting stronger," says Born, who studies sleep and memory at the University of Tübingen in Germany. "Memories are reactivated and reprocessed."

And just what is it about the sleeping brain that makes it a memory machine? "We don't know how it does any of this," says Stickgold, "because no one knows how a memory is formed." But that is not going to stop scientists from trying to find out. Working in humans and animal models, researchers are documenting how the sleeping brain behaves, and trying to link that activity to the vast and complex constellation of information it stores.

MEMORY MAKER

A night's sleep has five distinct phases, which the brain cycles through roughly every 90 minutes. In rapid eye movement (REM) sleep, the brain's electrical activity looks much as it does when someone is awake. Researchers assumed that REM was when dreams took place — and that in dreams, perhaps, memories are consolidated, the brain replaying the day's experiences and storing them as enduring recollections.

In support of this idea, in the mid-1990s, researchers at the Weizmann Institute of Science in Rehovot, Israel, showed that sleep helped to improve learning. People performing a task that involved searching a screen for symbols were better at it after they had slept, and that boost particularly correlated with REM sleep[1]. The finding triggered an interest in searching sleep for the root of memory.

But it is clear now that memory processing — and even dreaming — are not the exclusive preserve of REM sleep. The REM phase may help us deal with the emotional processing that memories often need (see 'The dark night', page S14). But much of the legwork of memory is done during other phases of sleep — helping the brain shuffle memories around, reactivating them in the hippocampus, editing them in areas such as the prefrontal cortex, and returning them to areas of the cortex nearer the hippocampus for longer-term storage and retrieval (see 'The anatomy of sleep', page S2). "All parts of sleep contribute in some way," says Matthew Wilson, a neuroscientist at the Massachusetts Institute of Technology (MIT) in Cambridge.

Since the late 1990s, many researchers have been concentrating on the role of slow-wave sleep in memory. Slow-wave sleep is a phase of deep sleep in which the cortex produces very low-frequency electrical oscillations of around 1 Hz that spread through the brain.

The shift in focus to slow-wave sleep is not necessarily because it is more interesting than REM, but it is easier to study. Brain activity is at a more consistent level, and the patterns of activity found in slow-wave sleep can be more

readily tied to recent experience. In rats, for example, the same patterns of activity can be seen while the animals explore a maze and when they later sleep. "Non-REM sleep has been more accessible physiologically," Wilson says. "That's where the data are."

There is now plenty of evidence that slow-wave sleep helps consolidate memories. Born's experiments show that brain regions coordinate their slow-wave activity during sleep in people who have been asked to learn lists of word associations[2]. Synchronizing the activity of groups of neurons is thought to be one way in which the brain gets different areas to cooperate to encode new information.

By contrast, disordered sleep may lead to disordered memory. Stickgold's team has shown that people with schizophrenia have fewer sleep 'spindles' — half-second bursts of activity in stage 2 non-REM sleep, the stage before slow-wave sleep. Perhaps as a result, these patients recall learned movements less easily the following day than non-schizophrenic sleepers[3].

JAMES HOLMES/SCIENCE PHOTO LIBRARY

CHASING THE TRACE

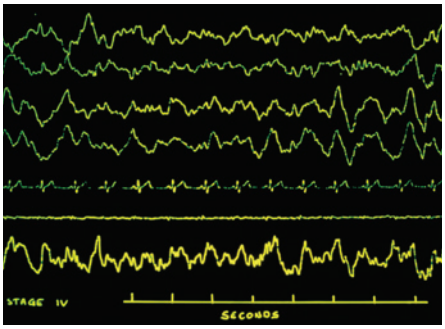
Nobody really knows how these oscillations in brain activity during sleep act at the cellular level to strengthen memory traces. But then, memory in general remains frustratingly mysterious. "If we could pinpoint the location of a single memory," says Stickgold, "we could figure out how sleep changes it."

Work in animals is helping to solve the puzzle. Scientists can insert electrodes that record directly from neurons in a brain region such as the hippocampus, bringing them one step closer to the action than monitoring brain oscillations, which are produced by lots of neurons firing at once. "Animal work gives you access to the basic mechanisms and the degree of control required to test hypotheses," says Wilson, who studies rats.

The evidence so far indicates that, in animals, slow oscillations happen when cells in the hippocampus are busy replaying recollections from the day. For example, in the rat brain, researchers recorded patterns of activity that looked like memories being played back, at the same time as they saw slow oscillations, suggesting that they are functionally linked. Assuming that, at the basic neuronal level, human memory is not radically different to that of lab animals, a similar process could occur during human slow-wave sleep.

At MIT, Wilson and his colleague Daniel Bendor have taken the study of memory one step further. They showed it was possible to influence memory replay in sleeping rats, using cues to prompt and consolidate specific memories[4]. "That's always been the holy grail, to demonstrate the link between memories and specific behaviours," says Wilson. They trained rats to run to the left or right of a track, depending on which of two tones was played. Then, while the rats were asleep, they recorded electrical activity directly from neurons in the hippocampus. By playing a tone associated with the left or right turn, they could influence the replay of the rats' spatial memory of the maze — in essence, manipulating the rats' 'dream' of turning left or right.

Wilson, Bendor and others now want to go beyond the hippocampus, looking at how memories are stored elsewhere. "The story that everyone tells is that sleep is important for transferring memories to the rest of the brain,"



Brain and muscle activity traces in slow-wave sleep.

says Loren Frank, who studies memory at the University of California, San Francisco. "But the problem is there's basically no direct evidence for this idea." There are indirect hints from functional magnetic resonance imaging (fMRI) studies that memories are transferred via an inner brain region called the striatum to the cortex for long-term storage, but the pathway still needs to be confirmed.

SLEEP TIGHT

How much time your brain spends in slow-wave mode could influence the value of a night's sleep. Children spend more time in slow-wave sleep than adults, and Born wanted to see if this made a difference to how they recalled a task.

In a study published earlier this year, Born and colleagues asked children and adults to press a sequence of buttons depending on which one was lit at the time. Then they let them sleep. In the morning, both groups were asked to recall the series from memory, without performing the task. Children were better at converting their practice of the task, which gave them implicit knowledge about the sequence, as shown by the decreasing time it took them to press the buttons, to explicit knowledge about it — a memory of the task sequence they could reproduce on demand[5]. This greater explicit knowledge was linked to children's greater slow-wave activity, suggesting that adults who spend longer in slow-wave sleep could reap the benefits too.

Work from neuroscientist Matthew Walker's lab at the University of California, Berkeley, focuses on what happens to memory in our twilight years. "We know as we get older our ability for learning and memory gets worse," Walker says. His team wanted to know whether the decline had anything to do with sleep (see 'Amyloid awakenings', page S19). A study using recordings of electrical brain activity during sleep, and fMRI after sleep to investigate patterns of brain activity during recall of a task, suggested that we are no longer as efficient at laying down new memories as we age. A reduction in the amount of deep, slow-wave sleep seems to be crucial[6]. "Older people can't generate the depth of sleep — so they can't hit the 'save' button so easily."

Older brains may be losing their plasticity — the ability to adapt and change dependent on experience, which underlies learning. Neuroscientist Marcos Frank at the University of Pennsylvania in Philadelphia has shown how sleep and plasticity interact in cats. He covered one of the cats' eyes during a critical period of development when they were a month old, and looked at the difference in the visual cortex in animals that were sleep deprived or allowed to sleep normally. In the cats allowed to sleep, the visual cortex responded more to input from the remaining open eye. But in the sleep-deprived cats, this consolidation process was blocked[7].

A DAY TO REMEMBER

Sleep is not the only time that memories are processed. Loren Frank and his colleague Mattias Karlsson showed that rats reactivate memories and consolidate them even while they are awake and quietly resting[8]. They are now studying what differences there might be between reactivations in a waking versus a sleeping state.

Wilson agrees that sleep, rest and anything in between might have different roles in memory processing. "The question is not 'is it processed or not', but how is it processed differently in these different states?" And he has even more ambitious goals for sleep researchers. "In studying sleep," he says, "we should be able to come to a new understanding of what memory is."

If we understand it better, perhaps we can use that knowledge to make our memories sharper. Born's lab has already used low-level electrical stimulation to boost people's memory. Just last month they showed that synchronized sounds can enhance slow waves during sleep and increase memory for word pairs[9]. In the meantime, there is no denying the importance of a good night's sleep. And, for Born's eight-month-old daughter, the importance of spending most of your infancy with your eyes shut. ■

Kerri Smith *is senior audio editor for* Nature.

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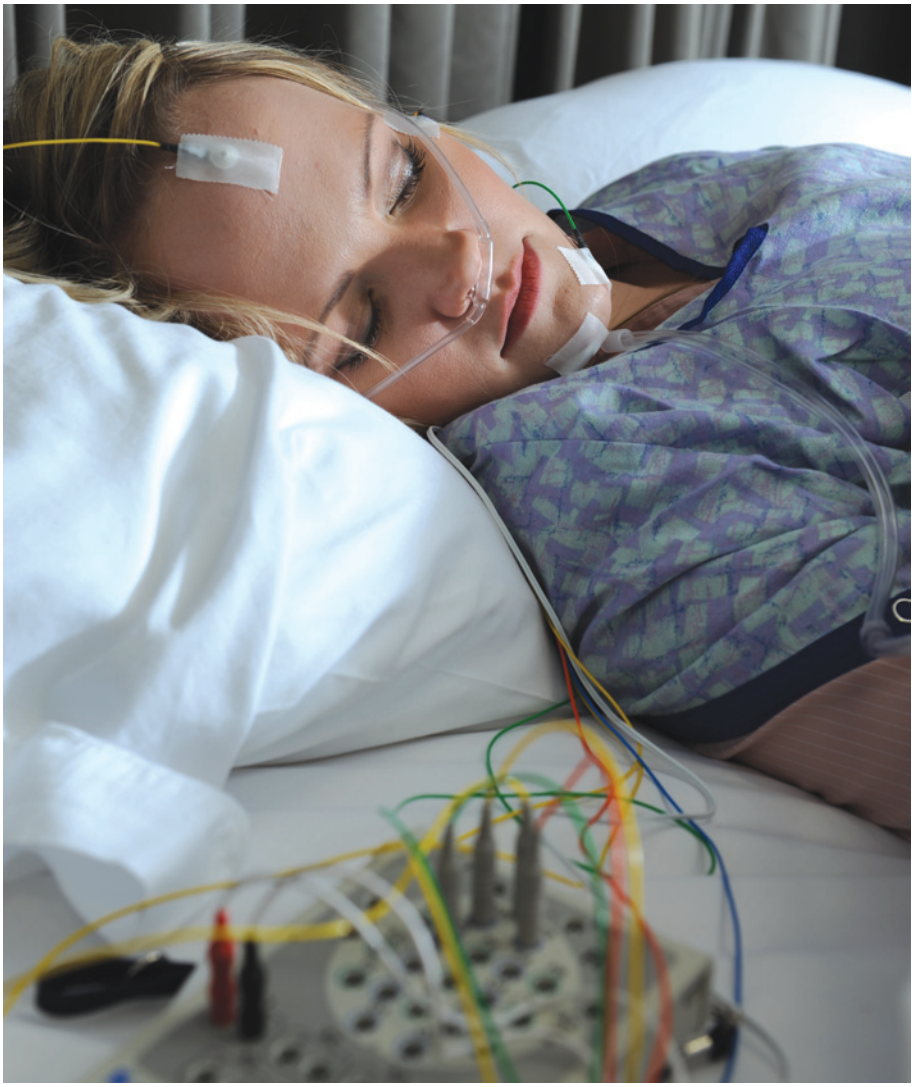

UNIVERSITY OF CHICAGO

Clinic-based studies allow researchers to control sleeping time and monitor any physiological changes.

DEPRIVATION

A wake-up call

Studies that restrict sleep show why a lack of shut-eye can lead to serious chronic disease.

BY ELIE DOLGIN

What happens when people go to bed is usually a private matter. But on the eighth floor of the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, sleep is a closely watched affair. Gold-cupped electrodes stuck to the faces and scalps of study participants monitor brain activity; wrist sensors detect movement; and finger cuffs track blood pressure. Even the flicker of an eye is registered, and bodily waste is treated as a commodity — all under the constant supervision of study coordinators.

On a Friday morning in February, researchers are busy cleaning up after the last participants and readying the ward for the next test subjects, who are due to arrive that afternoon. Two by two, trial participants come to the Harvard Catalyst Clinical Research Center here for a three-week 'sleep-over'. After a few nights of acclimation, each pair is randomly assigned either a full eight hours of sleep per night or recurring bouts of short sleep: three nights of four hours followed by a single night of eight hours, repeated for four cycles, with a recovery period of full sleep afterwards.

"We are trying to understand how physiological systems are altered if insufficient sleep goes on for a long time," says Janet Mullington, director of the BIDMC's Human Sleep and Inflammatory Systems Research Unit, who is leading the study. This 22-day trial is one of the longest of its kind to date.

Historically, most controlled sleep studies were short in duration but extreme in deprivation: volunteers were kept awake for periods ranging from 24 hours to five days in a row. Such acute sleep-deprivation trials have shown how sleep loss alters several mediators of inflammation, metabolism and other physiological pathways.

However, researchers worried that these all-night studies did not replicate one of the major sleep habits of modern life: getting some sleep each night, but not enough. According to the US Centers for Disease Control and Prevention, 30% of US workers get fewer than 6 hours of sleep per day[1] — far below the 7–9 hours that most experts recommend based on the existing evidence.

To find out what happens to someone getting fewer hours of sleep than recommended each night, scientists began to run longer trials, typically lasting a week or two, including repeated bouts of reduced or 'partial' sleep time. "What we will learn from these partial sleep-deprivation studies is in some ways more immediately transferable to real-world situations," says Mullington.

Prior epidemiological studies resulted in the first data linking people who tended to sleep less with increased rates of obesity, diabetes, cardiovascular disease, cancer and ultimately death. Now sleep researchers hope that controlled sleep-restriction studies can reveal the underlying mechanisms.

ILL EFFECTS

The first study to investigate the ill effects of persistent partial sleep loss in a controlled setting was published in 1999 by Eve Van Cauter and her colleagues at the University of Chicago in Illinois. In that study, 11 young men were restricted to four hours of sleep a night for six consecutive nights. The researchers then measured the subjects' blood glucose levels and rates of insulin secretion in response to glucose. They found that both measures of sugar metabolism fell by about a third after the sleep deprivation[2].

More recently, Van Cauter's team has identified a molecular culprit for this metabolic impairment. They collected abdominal fat cells from study participants who slept just 4.5 hours per night for four nights in a row, and then again after four nights of full sleep, looking in particular at whether AKT, a key protein involved in insulin signalling, was in its active state in the fat cells. They found that AKT activity was much lower after the short sleep than after the full sleep — the reduced AKT levels were similar to those found in people with insulin resistance, obesity and type 2 diabetes (see

'Heavy sleepers', page S8). Restricting sleep is equivalent "to a change in weight of about 10 kilograms", says Van Cauter, who reported the findings[3] last year. "It's a big effect and it can happen quite quickly."

DIVERSE PROBLEMS

Experimental sleep restriction is also uncovering health problems unconnected to metabolism. A 2003 study by Mullington and psychiatrist David Dinges, of the University of Pennsylvania's Perelman School of Medicine in Philadelphia, showed that sleeping for only 4 or 6 hours over 14 consecutive nights impairs people's alertness and performance in several cognitive tests[4]. Mullington and her BIDMC colleague Monika Haack later found that limiting participants' sleep to 4 hours per night for 12 nights can affect the immune system too[5]. Towards the end of the experiment, sleep-deprived individuals showed elevated blood levels of the immune signalling molecules interleukin-6 (IL-6) and C-reactive protein (CRP), both of which have been linked to inflammatory problems such as coronary artery disease.

"Even this modest sleep restriction creates a condition of low-grade inflammation," says Alexandros Vgontzas, a psychiatrist and sleep specialist at Pennsylvania State University College of Medicine in Hershey, who conducted a similar, as yet unpublished, trial. "Numerous studies have shown that these markers when elevated are associated with atherosclerosis, heart problems, diabetes and the like. So, we speculate that if people do not sleep enough on a long-term basis, this creates a condition that may lead to cardio-metabolic problems."

The immune deficits resulting from poor sleep can also undermine people's responses to vaccines. Last year, a team led by psychologist Aric Prather from the University of California, San Francisco, reported that 26.4% of middle-aged adults who slept fewer than 6 hours per night were not clinically protected against hepatitis B six months after receiving the standard three-dose vaccine series, compared with only 3.4% of those who slept more than 7 hours a night[6]. "This adds to our growing understanding of adding sleep to the cadre of important healthy behaviours," says Prather.

Too much sleep can also be a problem, though. In 2009, Sanjay Patel and Susan Redline, both now at the Brigham and Women's Hospital in Boston, Massachusetts, showed[7] that people who say they sleep more than eight hours per night have elevated blood levels of IL-6, CRP and tumour necrosis factor-α, another cytokine involved in systemic inflammation. Now Michael Irwin, a psychoneuroimmunologist in the David Geffen School of Medicine at the University of California, Los Angeles, is leading a study designed to test whether cutting back on excess sleep can reduce these inflammatory markers.

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For some of the latest results on sleep restriction:
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The search for why sleep patterns can be unhealthy has recently moved deeper, to the activity of DNA. In a study published earlier this year by a team at the University of Surrey in Guildford, UK, 26 healthy participants slept for at least 8 hours per night for one week and just under 6 hours per night for another. After each week, they were kept awake for about 40 hours in a row while the researchers, led by Derk-Jan Dijk, measured gene expression levels in the subjects' blood cells.

A week of insufficient sleep altered the activity of 711 genes, the authors found[8]. As expected, the genes affected included those involved with stress responses, the immune system and cellular metabolism. However, the restricted sleep also affected several genes involved in overall gene regulation and chromatin remodelling, suggesting that chronic sleep loss could lead to many more negative changes than researchers previously recognized. What's more, the number of genes that responded to a subsequent night without any sleep jumped from 122 when the subjects were fully rested to 856 after a week of restricted sleep.

"Even this modest sleep restriction creates a condition of low-grade inflammation."

Such studies of the 'transcriptome' — exploring all the changes in gene activity in response to reduced sleep, for example — can yield much broader insights than simply considering one aspect of physiology, notes Mehdi Tafti, a neurogeneticist who studies sleep at the University of Lausanne in Switzerland. "It gives a much more global view of the changes going on because of sleep deprivation," he says.

Genetic differences have also been found to underlie variation between individuals in their response to partial sleep deprivation. For example, Dinges and Namni Goel at the University of Pennsylvania have linked a particular variant of a gene that encodes a cell surface marker involved in innate immune responses with sleepiness and fatigue levels — but not cognitive deficits — in healthy participants who were forced to sleep for only 4 hours per night for five nights in a row[9]. "Subjects who are positive for this allele are more vulnerable to the effects of sleep loss," says Goel, noting that the variant is found in 20–30% of the population.

PRESSURE TO CHANGE

Attention is now shifting to how doctors can use the information garnered from controlled sleep studies to improve the wellbeing of patients. Haack and Mullington conducted a proof-of-concept study, published last year, in which 13 people with early signs of hypertension (high blood pressure) who habitually slept for fewer than 7 hours per night extended their sleep by one hour per night for six consecutive weeks, while another 9 people maintained their usual sleeping habits. At the end of the trial, those who had the extra sleep saw their average blood pressure readings drop from 142/82 to 128/74; in contrast, those who made no change experienced no significant reduction in blood pressure[10].

This study is already altering the behaviour of at least one individual, notes Haack. "One of our participants decided to continue with the extended bedtimes even after the study was over, and proudly reported that his cardiologist was able to lower his blood pressure medication," she says.

SLEEP WELL

People whose lack of sleep could be damaging their health could benefit from drug treatments, although figuring out which drugs will help which people is a challenge. "If we were able to use a biomarker or a functional assay and identify those individuals who are not getting enough sleep and are at risk of adverse health outcomes, that could really help us give people feedback and perhaps target the mechanistic pathways," says Redline. "Maybe they would be more likely to benefit from an anti-inflammatory agent, or a lipid-control medication."

Drugs of this sort could help to mitigate the consequences of sleeplessness or poor sleep quality, but they are unlikely to be the perfect solution, researchers warn. "Because of the multiplicity of pathways, I cannot imagine a single pharmacological approach that will prevent the adverse effects of insufficient sleep," says Van Cauter. "You are not going to have a magic pill."

Ultimately, this research points to an obvious conclusion: we need to sleep well now to avoid health problems later. "It's almost like this is common sense," says Virend Somers, a cardiologist at the Mayo Clinic in Rochester, Minnesota, who studies the effects of sleep loss. "But sometimes when you show people hard and fast scientific data, show them the numbers and show them the experimental evidence, it becomes more forceful." ■

Elie Dolgin *is senior news editor of* Nature Medicine *in Cambridge, Massachusetts.*

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EMILIANO PONZI

OBESITY

Heavy sleepers

A growing body of evidence shows that getting a good night's sleep plays an important role in regulating the body's metabolism.

BY BRIAN OWENS

Burning the midnight oil can leave you tired and grumpy the next day, dulling your mind and slowing your reaction times. But lack of sleep has consequences beyond the brain as well, with long-term sleep disturbances leading to metabolic problems.

Matthew Brady, a biologist at the University of Chicago in Illinois who studies the links between sleep and metabolism, puts it simply: "Fat cells need their sleep as well."

Many large population studies over the past decade have found that people who sleep poorly are more likely to be obese and to have metabolic disorders such as type 2 diabetes. One study of more than 1,000 people found that sleeping for only 5 hours rather than 8 hours results in a 3.6% increase in body mass index.

There is evidence that it's this lack of sleep that causes metabolic disorders and weight gain. In 1999, Eve Van Cauter and her colleagues at the University of Chicago showed that sleep restriction in healthy young men led to signs of insulin resistance, which can lead to type 2 diabetes. This finding "changed the entire world of sleep" research, says Fred Turek, who studies the biology of circadian rhythms at Northwestern University in Evanston, Illinois. Before Van Cauter's research, the only known effect of a lack of sleep was that "you were tired", Turek says, but the study revealed that "people getting too little sleep are at risk of obesity, diabetes and other metabolic disorders."

The underlying biology is slowly becoming clear. Van Cauter's work helped to show that two hormones — leptin and ghrelin — are likely to be involved in the link between sleep and weight gain. Leptin is produced by fat cells and is a signal of satiety; ghrelin is produced by the stomach and signals hunger. Together, these hormones regulate hunger and appetite. Van Cauter's team later showed that restricting the sleep time of healthy young men in the lab caused their leptin levels to fall and their ghrelin levels to rise, increasing their appetite, especially for fatty and sugary foods[1].

The biochemical pathway that leads from lack of sleep to changes in leptin and ghrelin levels is still being investigated, says Esra Tasali of the University of Chicago, who worked with Van Cauter on the leptin–ghrelin study. Tantalizing clues emerged from a study published in 2012 by Tasali, Brady and Van Cauter showing that reduced sleep leads to increased insulin resistance in fat cells. The effect was huge: after four nights of just 4.5 hours of sleep, the fat cells of young, healthy volunteers showed a 30% reduction in insulin sensitivity[2]. That's "the equivalent of metabolically ageing them 10 to 20 years", says Brady.

So reducing sleep can have a profound effect on individual cells. "The fat cell's getting some signal saying 'I'm not sleeping much', and that's going to alter its biology," says Turek.

Metabolically, sleep quality is just as important as sleep duration. The onset of slow-wave sleep coincides with hormonal changes that

affect glucose regulation, such as the release of growth hormone. When people are allowed to sleep for 7 or 8 hours, but are prevented for several consecutive nights from going into deep, slow-wave sleep, they show the same insulin signalling response as if they had been sleeping for only 4 hours.

The link between sleep and metabolism might be controlled by a part of the autonomic nervous system called the sympathetic nervous system, says Tasali. Activity of the sympathetic nervous system inhibits digestion, and so suppresses the secretion of insulin from the pancreas. Brady adds that because leptin levels are proportional to insulin-stimulated glucose uptake in fat cells, a reduction in insulin sensitivity could lead to less leptin production, which would in turn stimulate appetite and potentially lead to weight gain.

WE'VE GOT RHYTHM

The interaction between sleep and metabolism is complicated by the poorly understood relationship between sleep and the body's natural circadian rhythms. "If you disrupt circadian rhythmicity, you're going to have effects on the sleep–wake cycle," says Turek. "And if you disrupt the sleep–wake cycle, you're probably having effects on various circadian rhythms as well."

The circadian rhythm is determined by a collection of interrelated biochemical clocks that influence when we sleep, when we eat, and many other biological activities (see 'Stepping out of time', page S10). Mice that lack a working copy of a protein called Clock develop high blood sugar and cholesterol levels and low insulin, eventually becoming obese[3].

The Clock protein is active in a brain region known as the suprachiasmatic nucleus (SCN), which is linked to the light–dark cycle of day and night. The SCN synchronizes all the body's 24-hour clocks, either directly, for example by stimulating the pineal gland to produce the hormone melatonin, or indirectly, by influencing the time of feeding, which activates pancreatic function. But, says Turek, "humans are the only species that doesn't pay attention to their biological clock" — we eat whenever we want.

To study the metabolic effect of eating at different times, Turek altered the natural feeding time of mice. He fed one group of mice a high-fat diet only during the day, when these nocturnal animals would not normally be eating, and fed another group the same diet only at their biologically normal time, at night. The results sound a cautionary note to those of us who consistently fall out of sync with our body's natural eating schedule. Although both groups of mice consumed the same amount of calories and had similar levels of activity, after six weeks the animals fed during the day had gained significantly more weight and had more body fat than those fed at night. "Eating at the wrong time of day leads to alterations in something — maybe basal metabolic rate, maybe body temperature — that changes how the body processes the energy that it takes in," he says. "If you're eating at the wrong time of day, you're more likely to gain weight."

So when humans override the SCN's signal by eating late at night, they throw their feeding cycle and various downstream rhythms out of alignment with the central nervous system, with possible knock-on consequences for their metabolism. "It's not only what you eat, it's when you eat," says Turek.

SLEEP IT OFF

It's clear then that bad or shortened sleep causes metabolic problems. But would getting more and better sleep reverse these effects — for example, by helping obese people to lose weight? Research by Tasali and others suggests that such therapeutic effects are possible.

Tasali has focused on improving sleep quality in pre-diabetic patients who suffer from sleep apnoea, a breathing disorder that leads to disturbed sleep. "We can give them back their sleep quality by treating their sleep apnoea, and see what happens to their glucose metabolism," she says. In a study presented at the American Thoracic Society meeting in Philadelphia, she found that a two-week regimen of the standard treatment for sleep apnoea, called continuous positive airway pressure, led to greatly reduced insulin resistance[4].

"If you're eating at the wrong time of day, you're more likely to gain weight."

Similarly encouraging results have come from weight-loss research. Obesity specialist Giovanni Cizza at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, has been testing whether overweight people who are short sleepers can lose weight if they are coached to sleep longer[5]. The study ended in 2012 and Cizza is now analysing the data. He says he is "pleased" with the results, despite a major hiccup in the trial.

The subjects were split into an intervention group, in which subjects were coached about good sleep hygiene and how to improve their sleep habits, and a comparison group, given no coaching. But simply making the comparison group more aware of their sleep habits, by asking them to fill out sleep diaries, helped them extend their sleep duration by almost as much as the intervention group. Basically, Cizza says, "my placebo group took the drug too". The results have not yet been published, so he would not say how much weight the subjects lost — only that because both groups extended their sleep, there was no significant difference between them in sleep duration or weight loss.

Clearly, the relationship between sleep and metabolism is complicated. A host of interacting biological, behavioural and psychological factors influence both sleep and metabolic function, says Jim Horne, a sleep researcher at Loughborough University, UK. People who sleep less have more time to spend eating, for example. The stress and tiredness caused by a bad night's sleep can lead to comfort eating and less activity during the day. In addition, obesity is known to cause breathing problems, such as sleep apnoea, that can interrupt sleep. And both poor sleep and obesity are often associated with other disorders, such as depression (see 'The dark night', page S14).

As a result, it is unclear whether short sleep duration causes obesity, or vice versa, says Horne. "I challenge this idea that short sleep makes you fat. I would say being fat causes short sleep and bad sleep."

But it may not be necessary to untangle cause and effect fully before testing the simple proposition of whether better sleep can help people lose weight. Because sleep is not a drug, testing its effects should be a less daunting process than that required for pharmaceutical development, says Cizza. After all, he points out, if you're not getting enough sleep, getting more will have no adverse side effects, and will have many added benefits in terms of mood and neuropsychological function, for example. "Where there is reasonable evidence for efficacy and there is no harm, I think we should bring this to the public sooner than a drug."

Brady points out that people often find it difficult to change their diet and take more exercise. "Telling them to sleep more, we think that might be a little more palatable."

Horne, however, urges caution. In most cases, he says, the effect of extra sleep on metabolism is vanishingly small. "Fifteen minutes of brisk walking every day is far better at regulating your body weight than an extra hour of sleep, so we have to put things in perspective." He worries that people will be tempted to avoid healthy exercise in favour of the less strenuous option of popping sleeping pills, which do have side effects. That could be dangerous, and no one working on the complex relationship between sleep and metabolism would recommend trying such a shortcut.

But there is mounting evidence that getting the right amount of healthy sleep can be just as important as diet and exercise in controlling your metabolism, and can do a world of good beyond making you wake up happy in the morning. ■

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For more on the link between sleep and metabolism:
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CHRONOBIOLOGY

Stepping out of time

How can people better adapt to an 'unnatural' world of artificial lighting and alarm clocks?

BY MICHAEL EISENSTEIN

By the time Elizabeth Klerman boards the train to go to her office at Brigham & Women's Hospital in Boston, Massachusetts, the conductor has been awake for hours, rising in the dead of night for his first train at four o'clock. This schedule is not merely demanding, but contrary to most people's circadian rhythms, the pattern of physiological and metabolic activity that is roughly in synchrony with the rising and setting of the Sun.

"Some people are trying to live and work with an abnormal relationship between their circadian rhythm and the clock," says Klerman, who studies human sleep patterns. Most of us have experienced this mismatch in the form of jetlag. For shift-workers and others with 'unnatural' routines, however, this desynchronization occurs every day and can result in chronic sleep deficits. Researchers are now trying to understand the prevalence and severity of the problem, and to devise strategies that can help reset these clocks.

THE TIME MACHINE

Many body tissues have their own timetables, organized by cyclic oscillations in the expression of a network of numerous 'clock genes'. "The entire body is a clock," says Derk-Jan Dijk, director of the Surrey Sleep Research Centre in Guildford, UK. "It's a house with clocks in every room and every corner, yet in one way or another they work in an organized way." The timing of all these various 'peripheral oscillators' can profoundly affect metabolic activity, immune cell proliferation, and numerous other critical functions. But there is a central pacemaker that gives the body a sense of the time of day: the suprachiasmatic nucleus (SCN), a group of neurons in the hypothalamus (see 'The anatomy of sleep', page S2).

When melanopsin photoreceptors in the eye detect light, the SCN is activated and responds by initiating a host of rhythm-establishing physiological responses, including suppressing production of the hormone melatonin by the pineal gland (see 'The light switch'). The peripheral oscillators can be shifted by physical activity or by altering meal times, but most research suggests that light exposure is by far the most important determinant of rhythms driven by the SCN. "If you look at the data for humans, every time they suggested that exercise or food may shift the clock, they also suggest that light may have been involved," says Debra Skene, who studies chronobiology at the University of Surrey, UK.

Light is the dominant influence on circadian rhythms, but other factors can come into play. A small subset of completely blind people who lack melanopsin photoreceptors, for example, can still achieve some circadian entrainment through external cues and lifestyle[1]. This timetable can be shattered by a trip across a few time zones, however, requiring long periods of readjustment without the assistance of light to signal the time of day. Many other totally blind individuals fail to entrain at all, with profound effects. "They sleep at night because that's when they're told to sleep, so they have very short sleep of poor quality, and at lunchtime their circadian system starts saying they should go to sleep," says Skene. "So we see them extremely tired — they nap and they don't perform well."

BASIC INSTINCTS

Humans are diurnal animals and so tend to be active by day and rest at night. But personal preferences for when to sleep can differ considerably among individuals, and even at different stages in the same person's life — the difference between being early birds or night owls.

Researchers are still grappling with the best approach to measure the innate timing of someone's internal clock. As an indicator of 'biological night', levels of melatonin in various body fluids can give researchers a way to monitor the SCN cycle directly in an individual. But this requires repeated body fluid sampling over extended periods, and is therefore impractical for population-scale studies. Instead, most sleep

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Scientists tinker with our circadian clocks:
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Exposure to light after sunset tricks the body into thinking it's still daytime, delaying the onset of 'biological' night.

researchers rely on surveys in which people self-report their sleeping habits.

One of the biggest surveys of sleeping habits, with more than 150,000 respondents from around the world, is the Munich Chronotype Questionnaire (MCTQ), run by Till Roenneberg at the Ludwig Maximilians University in Munich, Germany. His team devised an online survey that asks people to describe the timing of their sleep behaviour on a day-to-day basis, both on normal working or school days and at weekends or holidays. By characterizing individual sleep patterns — what Roenneberg calls a 'chronotype' — it is possible to quantify habits previously observed only at an anecdotal level, such as the tendencies of children to wake early and of teenagers to sleep late. "We were able to show how drastically the clock gets later from childhood through adolescence, reaching peak lateness in women at 19-and-a-half and in men at 21, and after those ages people get earlier again until they die," says Roenneberg.

ALARM CLOCK SHOCK

The MCTQ data have also provided insights into how our biology is altered by living and working in the artificially illuminated, industrialized world[2]. By assessing both rural and urban populations, Roenneberg and others have shown how modern life scatters people's sleep patterns even further around the clock. "If we were all farmers, working outside all day, chronotypes would vary only by three to four hours," says Roenneberg. "But since most of us work predominantly indoors and use artificial light after sunset, our clocks don't receive strong synchronizing signals anymore, and chronotypes nowadays span up to 12 hours."

Circadian desynchrony is most acute in people whose work schedules make them live nocturnal lives. "They are exposed to a very complex light–dark cycle, where there is artificial light at night but still some natural light that you may see during the commute home or to work," says Dijk. "In the majority of those types of shift workers, their central clock does not adapt."

Roenneberg's team has found that circadian desynchrony may be far more pervasive, however. Many modern workers effectively live on two different timetables — one enforced by their weekday alarm clock, and the other aligned to their weekend socializing and 'sleeping in' — resulting in disruption that he has dubbed 'social jetlag'[3]. "In most people, it looks as if they were travelling from Europe to the United States on a Friday evening and back on a Monday morning, because their displacement is so large," says Roenneberg. This disconnect begins at adolescence, when our body clocks reach their latest preferred wake time, and continues all the way to retirement age.

People who operate on schedules not aligned to their internal rhythms, either due to shift work or social jetlag, often exhibit signs of chronic sleep restriction or disruption that can impair both job performance and overall wellbeing. "During wakefulness, you will have problems maintaining sustained attention," says Dijk. "You will be sleepier and experience disruption in working memory — you will see the effects across all cognitive domains."

In the long term, such desynchrony can exacerbate the risk of cardiovascular disease, obesity and other health problems[3,4] (see 'Heavy sleepers', page S8). "In our animal models of 'clock gene' mutations, we're seeing diabetes and a propensity for obesity and metabolic disorders," says Joseph Takahashi, who studies circadian rhythms at the University of Texas Southwestern Medical Center in Dallas. Several studies have found a similar connection in shift workers and other individuals operating on schedules not aligned to their internal rhythms[3,4]. These findings "don't necessarily mean that there are immediate health consequences", says Dijk, "but we can see the impact of being asleep or being awake at the wrong phase of your circadian cycle immediately."

BLUE IS THE COLOUR

At night, artificial lighting continues to activate the SCN and disrupt the natural release of melatonin, which normally heralds the onset of biological night (see 'Casting light on sleep deficiency', page S13). But not all light stimulates the SCN equally. Skene and others have shown that specific wavelengths are especially important 'waking' signals. "We observed peak light sensitivity at a wavelength of around 460 to 480 nanometres — a nice, deep blue," she says. Red light, by contrast, has only a weak impact on melanopsin receptors and is less prone to stimulate wakefulness. So adjusting the relative levels of blue and red light that people are exposed to throughout the day could preserve normal circadian timing even during prolonged exposure to artificial light.

Klerman is collaborating with her colleague Steven Lockley at Brigham & Women's Hospital and with George Brainard of Thomas Jefferson University in Philadelphia, Pennsylvania, to test this approach in an extreme situation: the International Space Station. Long-term isolation in cramped quarters poses many problems for astronauts, and they also experience disorienting light–dark cycles resulting from the station's orbital time of 90 minutes. "This is too short for our circadian system to synchronize," says Lockley. "The body clock starts to free run on

its own time, just like for blind people." This is further confounded by the need to interact with people operating on various Earth schedules, such as mission control in the United States or crews arriving from Russia.

Lockley and colleagues previously showed that blue light could help to synchronize Earth-based crews with the Martian day as part of the Phoenix Mars Lander mission[5]. The researchers are now exploring programmable LED (light-emitting diode) systems that dynamically shift from blue-enriched to red-enriched white light on a 24-hour cycle. "We're working on shifting people's rhythms more quickly and maintaining their alertness at a better level," says Lockley.

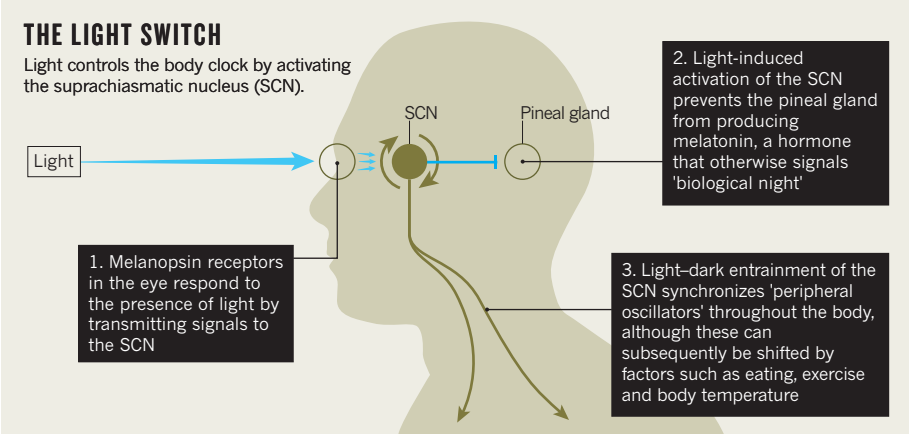
This technology may be most valuable in extreme places such as spacecraft, submarines or Antarctic research facilities, but the broader potential is obvious. The electronics company Philips, based in Amsterdam, the Netherlands, is one of several developing controllable, dynamic lighting systems for homes, schools and offices that boost blue wavelengths early in the day and in the post-lunch slump, and shift to redder wavelengths later in the afternoon.

A DOSE OF RHYTHM

It is not yet known whether these lighting systems will be effective in groups composed of people with widely varying chronotypes, but drugs that tinker with circadian rhythms could provide a more personalized approach. The hormone melatonin may not be sufficient by itself to send someone to sleep, but it nevertheless helps the body to prepare for sleep, and there is evidence it can affect the timing of sleep. "The general consensus is that melatonin can phase-shift circadian rhythms when properly applied," says Klerman. Indeed, a growing body of work suggests that the combination of properly timed melatonin dosing and managed light exposure can counter the circadian problems associated with both jetlag and shift work[6].

Melatonin requires a prescription in Europe but is available over the counter at health-food stores in the United States. However, the US Food and Drug Administration has limited oversight over the quality and content of such 'natural supplements', so it is difficult for US consumers to achieve correct dosing. As a more reliable alternative, several drug companies are developing synthetic agents that mimic the effects of melatonin, such as tasimelteon, developed by Vanda Pharmaceuticals in Washington, DC. Klerman and colleagues have shown that tasimelteon can improve sleep quality in time-shifted human subjects[7], and it is now in a phase III clinical trial for use in blind individuals who lack melanopsin receptors. Such people "have recurrent jetlag", says Klerman, "so they are an ideal population that you would want to try to entrain with melatonin agonists."

Several other potential circadian modulators have been discovered in the past two years. Pharmacology researcher Thomas Burris and colleagues at the Scripps Research Institute in Jupiter, Florida, identified two compounds, for example, that alter circadian rhythms by acting on a key regulator of clock gene activity. These compounds, known as SR9009 and SR9011, also affect weight gain and metabolism in mice[8]. "Small molecules that can reset the clock might help in recovering from jetlag more rapidly," says Takahashi, who collaborated with the Burris team and has launched a circadian drug-discovery company, Reset Therapeutics, based in Burlingame, California. He adds that circadian drugs could potentially treat metabolic problems associated with off-kilter body clocks, and counter the disturbed sleep that commonly afflicts elderly people.



"I'm not comfortable with using medication to align people to what society wants."

It is less clear whether these drugs would be an appropriate solution for chronic, lifestyle-associated jetlag, however. "Medication should be used if people are sick," says Roenneberg. "I'm not comfortable with using medication to align people to what society wants." As an alternative, he recommends designing work schedules to suit individual employees and their particular chronotype, which can be determined by questionnaires such as the MCTQ.

SMART SCHEDULES

Several industries are already using smarter schedules and training methodologies that maximize the health, performance and efficiency of their workers. Major corporations such as Procter & Gamble and Goldman Sachs are using 'sleep hygiene' programmes based on circadian research to keep their personnel sharp — for example, coaching staff to optimize their individual sleep schedules, and to switch off laptops and e-readers in advance of bedtime. The need for such efforts is especially keen in industries with round-the-clock operations — particularly those where working while tired could prove fatal, such as mining or manufacturing. In aviation, the US Federal Aviation Administration has recently put in place 'fatigue risk management systems' that aim to improve the safety of air travel by using carefully regulated work schedules and mandated rest time to minimize flight-crew fatigue.

However, Lockley questions the wisdom of retraining the public to adapt to schedules that are contrary to their biological needs. "Where we have to have 24/7 society — in health and safety services, for example — we should do it," he says. "But we should critically review whether we need 24-hour supermarkets or TV."

To help people make the most of their sleep while also leading happy and productive lives, we need a better sense of what natural human sleep patterns really are, and how our lifestyles reshape them. But this requires more data. Several research groups are now working with pre-industrial communities in the Amazon to get a better understanding of how the natural human clock runs in a non-electric world. Meanwhile, Roenneberg hopes to build on the success of the MCTQ with a much broader Human Sleep Project that will bring together leading sleep researchers to characterize circadian rhythms and sleep patterns at the population scale.

Waking up early to start work at four o'clock in the morning may never be entirely natural for people such as Klerman's train conductor, but better insights into sleep management could make such schedules more comfortable and the transition from weekend to the working week less jarring. "We need huge databases where thousands to millions of people have contributed data from their daily life," says Roenneberg. "Once we understand that, we can change our society and technology so that people can sleep in their proper, individual sleep windows." ■

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PERSPECTIVE

Casting light on sleep deficiency

The use of electric lights at night is disrupting the sleep of more and more people, says **Charles Czeisler**.

There are many reasons why people get insufficient sleep in our 24/7 society, from early starts at work or school, or long commutes, to caffeine-rich food and drink. But the precipitating factor is an often unappreciated, technological breakthrough: the electric light. Without it, few people would use caffeine to stay awake at night. And light affects our circadian rhythms more powerfully than any drug.

Just as the ear has two functions (hearing and balance), so too does the eye. First, rods and cones enable sight; and second, intrinsically photosensitive retinal ganglion cells (ipRGCs) containing the photopigment melanopsin enable pupillary light responses, photic resetting of the circadian clock, and other sightless visual responses. Artificial light striking the retina between dusk and dawn exerts other physiological effects through sightless vision. It inhibits sleep-promoting neurons and activates arousal-promoting orexin neurons in the hypothalamus, and suppresses the nightly release of the soporific hormone melatonin. These factors reduce sleepiness, increase alertness and interfere with our sleep.

Paradoxically, the daily peak of waking energy driven by the brain's master circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus occurs not at the start but near the end of our usual waking day, providing us with a 'second wind' that keeps us going as the day wears on. Before the widespread use of electric light, people probably experienced that second wind in the mid-afternoon, keeping them going until night fell. But light exposure after sunset signals 'daytime' to the SCN, shifting the clock later, postponing the second wind and delaying the onset of melatonin secretion. As a result, many people are still checking e-mail, doing homework or watching TV at midnight, with hardly a clue that it is the middle of the solar night. Technology has effectively decoupled us from the natural 24-hour day to which our bodies evolved, driving us to go to bed later. And we use caffeine in the morning to rise as early as we ever did, putting the squeeze on sleep.

TECHNOLOGY HAS DECOUPLED US FROM THE 24-HOUR DAY TO WHICH OUR BODIES EVOLVED.

The more we light up our lives, the less we seem to sleep. As the cost of generating light has plummeted by two orders of magnitude over the past century, its consumption has increased accordingly. Between 1950 and 2000, for example, as the cost of light production fell sixfold, UK per capita light consumption rose fourfold. This increasing light consumption has paralleled the rise in sleep deficiency.

Today, 30% of all employed US adults and 44% of night workers report averaging less than 6 hours sleep per night[1], whereas 50 years ago less than 3% of the US adult population slept so little. Worldwide, children are sleeping about 1.2 hours less on school nights than a century ago[2]. Most of us also sleep at different times during the week than at weekends and holidays, inducing 'social jetlag', which further disrupts circadian rhythms (see 'Stepping out of time', page S10).

The US Institute of Medicine estimates that between 50 million and 70 million people in the United States suffer adverse health and safety consequences from sleep disorders and sleep deficiency[3], including greater risk of obesity, diabetes, heart disease, depression and stroke. The obesity boom has triggered a parallel epidemic of obstructive sleep apnoea, which disrupts sleep (see 'Heavy sleepers', page S8). Children become hyperactive rather than sleepy when they don't get enough sleep, and have difficulty focusing attention, so sleep deficiency may be mistaken for attention-deficit hyperactivity disorder (ADHD), an increasingly common condition now diagnosed in 19% of US boys of high-school age. Some 40% of people in the United States report that their sleep is often insufficient, with 25% reporting difficulty concentrating owing to fatigue. The WHO has even added night-shift work to its list of known and probable carcinogens. And the death toll from driving while tired is second only to that caused by drink driving.

The number of people with sleep deficiency seems destined to rise. With 19% of electricity consumption worldwide devoted to producing light, many governments are phasing out traditional incandescent light bulbs[4]. Energy efficient solid-state light-emitting diodes (LEDs) are now widely used in televisions and computer screens, laptops, tablets and hand-held devices, and will drive a further increase in per capita light consumption.

Solid-state white light is typically rich in blue light, and the colour composition matters. The ipRGCs are most sensitive to short-wavelength (blue and blue–green) light, so night-time exposure to LEDs is typically more disruptive to circadian rhythms, melatonin secretion and sleep than incandescent lighting.

But solid-state lighting could also provide some solutions. A solid-state white-light fixture can comprise multicoloured LEDs, so it is relatively easy to control not only the light intensity, but also the colour composition. The adverse effects of night-time light on sleep and circadian rhythms can be reduced by replacing blue-enriched light with red- or orange-enriched white light after sunset. Unfortunately, existing uses of this new-found colour control have tended to be wrong-headed: some airlines, for example, suffuse aircraft cabins with monochromatic blue light at night, the optimal colour for suppressing melatonin and disrupting sleep.

Sleep is essential to our physical and mental wellbeing, so it is vital that we learn more about the impact of light consumption and other ways our 24/7 society affects sleep, circadian rhythms and health. We must then use this knowledge to develop behavioural and technical interventions to mitigate these ill effects. It is time to reassess the early assurances of Thomas Edison that using electric light "is in no way harmful to health, nor does it affect the soundness of sleep". ■

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The author declares a conflict of interest: go.nature.com/ygtirj

EMILIANO PONZI

MOOD DISORDERS

The dark night

The causal relationships between lack of sleep and mood disorders remain murky. But one thing is clear as day: better sleep can have psychological benefits.

BY SARAH DEWEERDT

One of the few personal touches in psychiatrist Murray Raskind's small, windowless office is a yellowing photograph of a young man in military garb. The man is crouching on the ground, leaning against his rifle for balance, and looks up at the camera with haunted eyes. It is a portrait of a soldier suffering from combat-related post-traumatic stress disorder (PTSD).

The man in the photo is Don Hall, who fought in Vietnam during the brutal Tet Offensive in 1968. When Raskind met him in the mid-1990s, Hall was plagued by recurrent nightmares, replaying his combat experiences as if they were on videotape, night after night for nearly 30 years. "That's a hallmark of combat PTSD," says Raskind, director of the VA Northwest Mental Illness Research, Education and Clinical Center in Seattle, Washington, who discovered that a common blood-pressure medication can alleviate these nightmares.

The symptoms of PTSD include anger and irritability, feeling numb and detached, and difficulty concentrating. "But as far as the veterans are concerned, their problem is they can't sleep," Raskind says. "And when they have a bad night with nightmares, the next day they're in a bleak mood."

The role of combat nightmares in PTSD is particularly dramatic, but sleep abnormalities are associated with nearly all mood and anxiety disorders. Depression often leads to insomnia, or sometimes to sleeping more than normal or having trouble getting out of bed. During manic episodes, many people with bipolar disorder — a condition characterized by bouts of high-energy frenzy alternating with depression — seem to need very little sleep, getting by on just a few hours a night for days on end.

Sleep disruptions are so common that they even form part of the diagnostic criteria for these disorders. "Mood dysregulation and sleep dysregulation seem to go hand in hand," says Matthew Walker, a sleep researcher at the University of California, Berkeley.

DISTRESS SIGNALS

The link between sleep disruption and psychiatric disorders is well established, but the causal relationships are less clear. Do sleep disturbances trigger episodes of these disorders, or do mood and anxiety disorders lead to difficulty sleeping? Both could be true. "It's a two-way street," says Walker. It's also possible that some other underlying problem in the brain interferes with both mood and sleep.

There is ample evidence that sleep and mood are entangled at the very root. People who sleep poorly are more likely to develop depression than those who sleep well[1], for example. Insomnia is often the first symptom of an episode of depression to appear, and often the last to go. And treatments including antidepressants and psychotherapy are less effective in people with both depression and insomnia than in those with depression alone[2].

Loss of sleep also often heralds an episode of mania in bipolar disorder. Similarly, sleeping too much is linked to depressive episodes. One study found that depriving people with bipolar disorder of sleep triggered mania or hypomania — a less intense episode that often precedes mania — in about 10% of patients[3].

People with bipolar disorder and their unaffected relatives are also more likely to be night owls — they have what sleep researchers call a 'delayed sleep phase'. Such observations suggest there may be a circadian component to sleep disruptions in mood disorders (see 'Stepping out of time', page S10).

Bolstering the circadian link, some patients show a seasonal pattern of bipolar symptoms, says Ruth Benca, a psychiatrist at the University of Wisconsin in Madison. They exhibit peaks of suicidal behaviour in spring and autumn, when day length changes most rapidly.

But other patients with bipolar disorder may have normal circadian rhythms, despite showing extremely chaotic sleep patterns, says psychologist Ellen Frank at the University of Pittsburgh in Pennsylvania.

The sleep problems associated with mood disorders go beyond the usual tossing and turning. Electroencephalography (EEG) studies

reveal abnormalities not just in how much and when these patients sleep, but also in how their brains function during sleep. Compared with healthy people, bipolar disorder sufferers are more likely to show a variety of abnormalities, such as more time in light sleep and waking up more often. They therefore spend less time in the deepest phase of sleep, known as slow-wave or delta-wave sleep. "For whatever reason, their brains don't seem to be able to make these delta waves that we believe are associated with the restorative aspect of sleep," Frank says.

In another EEG study, Benca and colleagues found that people with depression do not show the expected change before and after sleep in a measure of brain function associated with slow-wave sleep. The brain's electrical response to a sound, known as an auditory evoked potential, is normally larger before sleep than on waking, but those with depression don't show this decline. "Depressed people's brains don't reset the same way between the night and the morning as the control subjects," Benca says.

This finding is striking, she adds, because the study participants did not have bad insomnia. But Benca cautions that these abnormalities may or may not be connected to the symptoms that people with mood disorders experience during the day. Perhaps sleep simply removes the variables and distractions of the daytime and reveals how the brains of people with mood disorders function differently overall.

NEGATIVE IMAGES

To untangle these relationships, scientists are probing the neural basis of the connection between sleep and emotional state. In one of the first such studies, Walker and his colleagues performed brain scans on healthy adults — some of whom were well rested while others had been kept awake for 35 hours — as they were shown a series of images ranging from neutral to gory and unpleasant, such as mutilated bodies or children with tumours.

Viewing negative images activates the amygdala, an area of the brain involved in the formation of memory associated with emotional events, such as frightening experiences, the researchers found. Both groups had similar reactions when shown neutral images, but the amygdala's response to the negative images was about 60% greater in the sleep-deprived group[4].

"When you take a healthy brain and take sleep away, you can produce patterns of brain activity that look not dissimilar to some psychiatric disorders," Walker says. Similar overactivity in the amygdala is also seen in mood disorders, and unpublished data from Walker's lab suggest that a lack of sleep can mimic some of the brain processes seen in anxiety disorder.

Paradoxically, some depressed patients who are deprived of sleep for a night have diminished symptoms the next day, suggesting an antidepressant effect. It is thought that sleep deprivation dampens excess activity in one area of the brain, the anterior cingulate cortex, which is characteristic of depression[5]. Once they can sleep again, the depression returns, so sleep deprivation isn't a viable treatment. But the finding has spurred research to find out which types of sleep are involved in this effect.

Some evidence points to rapid eye movement (REM) sleep. For example, tricyclic antidepressants are thought to work by disrupting REM sleep. In some cases, an antidepressant's efficacy is correlated with how well it suppresses REM sleep, Benca says. But this may not be the whole story. Benca's group showed that disrupting the ability to produce slow waves during deep sleep has an antidepressant effect[6], which "opens the possibility that somehow manipulations of slow-wave activity might be effective".

Research from Walker's lab suggests a possible mechanism for this effect. They found that when healthy but sleep-deprived people view a series of neutral or positive images, they classify more of the images as positive than people who are well rested[7]. They also show greater brain activity in the mesolimbic system, a brain network thought to be associated with reward, suggesting that a lack of sleep increases activity in the brain's pleasure centre. These results are the flip side to Walker's earlier finding of greater responses to negative images in his overtired volunteers: sleep deprivation increases what researchers call emotional reactivity in general.

DON HALL

A haunted-looking Don Hall in Vietnam.

OVERNIGHT IMPROVEMENT

The causal relationships between sleep and mood aren't yet clear, but the implication for treatment is: get people sleeping better. "These sleep problems are very modifiable," says Allison Harvey, a clinical psychologist at the University of California, Berkeley. "Simple, powerful behaviour modifications can yield fairly startling improvements in both the sleep and the disorder."

For example, Frank and her colleagues have developed an approach to treating bipolar disorder that encourages patients to keep to a regular daily schedule of waking up, eating, socializing and going to bed. This method, Frank says, "seems to be protective against new episodes of bipolar disorder, and to help people come out of their depression more quickly". That's particularly important, she adds, because although drugs can keep mania in check, bipolar depression is not as easily controlled.

Harvey and her colleagues have begun to apply similar principles to unipolar depression. She has unpublished data suggesting that patients who are coached to improve their sleep are less likely to have a relapse of depression. Another group has shown that using cognitive behavioural therapy to treat insomnia (see 'Chasing the dream', page S16) improves the effectiveness of treatment for depression[8].

Walker refers to sleep as "overnight therapy". In REM sleep — the phase in which most dreaming occurs — the brain's production of noradrenaline (also known as norepinephrine) shuts down. Noradrenaline is the brain's form of the stress hormone adrenaline, so its absence during REM sleep creates a soothing neurochemical environment in which the brain can process tumultuous events. "It essentially takes the sharp edges off these emotional experiences," Walker says.

This process goes awry in PTSD, he thinks, as PTSD sufferers have too much noradrenaline and not enough REM sleep. Interestingly, the treatment for trauma nightmares that Raskind discovered, a blood-pressure drug called prazosin, blocks noradrenaline receptors in the brain.

A couple of weeks after starting prazosin, Hall told Raskind he was sleeping through the night for the first time since his military service in Vietnam. "I thought, man, I didn't know I was such a good psychotherapist," Raskind recalls. "I was sure this was a placebo effect." But Raskind gave the drug to a second Vietnam veteran suffering from PTSD, and his nightmares got better too. Randomized trials have since shown that prazosin reduces trauma nightmares, improves sleep, and diminishes other symptoms of PTSD in combat veterans[9]. About 70,000 US army veterans now take the drug.

Raskind reports that as long as Hall continues taking prazosin, his nightmares are kept at bay. And it shows. Raskind keeps another photo in his office, from Hall's recent wedding, showing a man who looks older but also more at peace: a portrait of the role of a good night's sleep in healing the mind. "He looks a lot better here than he did with that furrowed brow," Raskind says. "Notice the brow difference — that's the prazosin effect." ■

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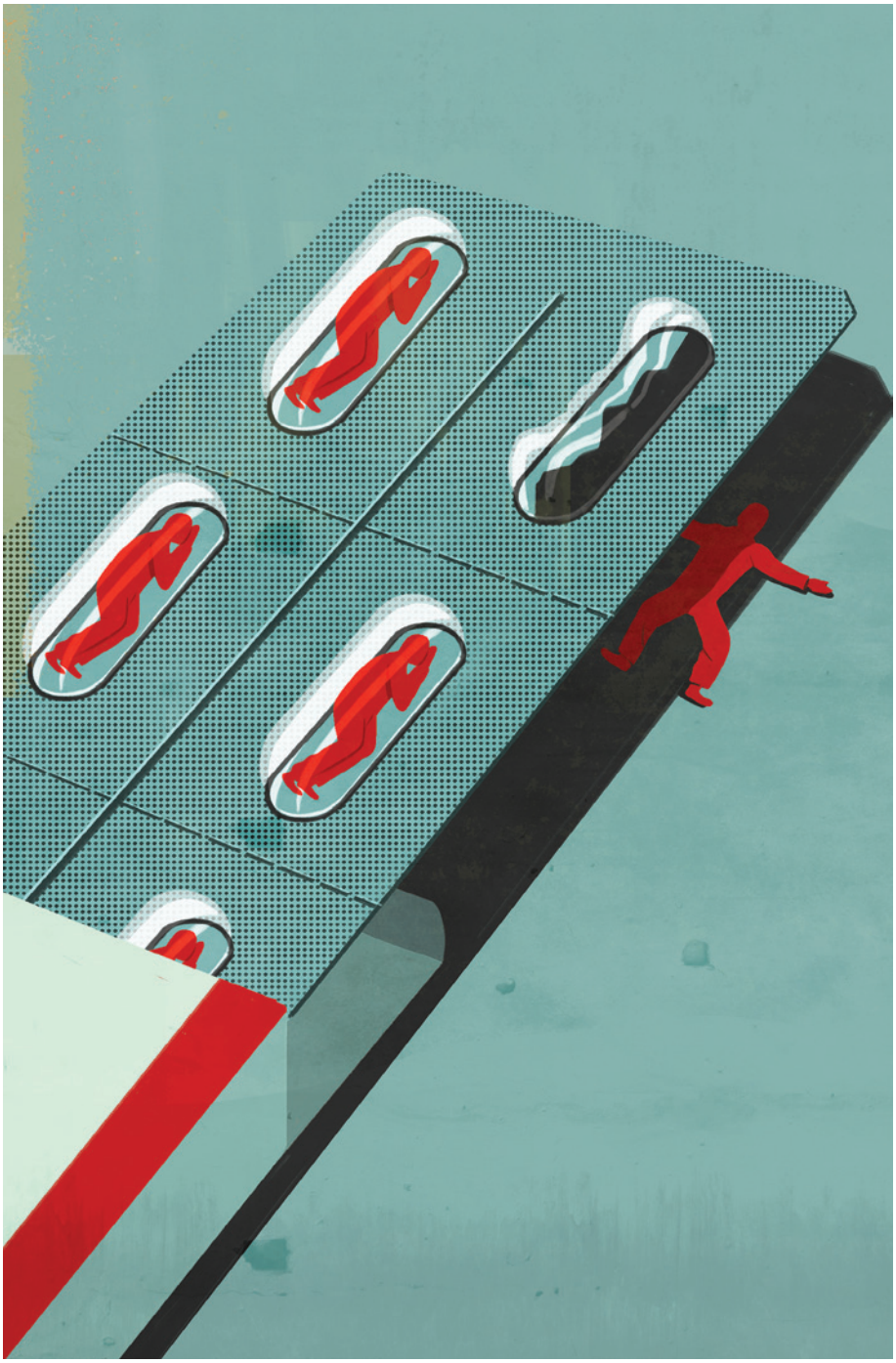

EMILIANO PONZI

INSOMNIA

Chasing the dream

A combination of drugs and cognitive behavioural therapy may finally put an end to the misery of sleepless nights.

BY JAMES MITCHELL CROW

How's your bedroom hygiene? If a sleep therapist asks you this, they aren't interested in your vacuuming habits or laundry routine. What concerns them is another form of detritus that tends to accumulate around our beds: the television across the room, the latest tension-building thriller just downloaded onto your e-reader, and the smartphone chirping the arrival of every new e-mail.

Practising sleep hygiene — cleaning gadgets, and anything else that promotes worry or alertness, out of the bedroom — is a proven technique that could help the huge numbers of people who routinely struggle to sleep.

One in three adults find it difficult to fall asleep, or stay asleep, at least one night a week[1]. Around half of those sleep so badly they have problems functioning during the day. "Insomnia must not be taken lightly, it is a very prevalent and significant public health problem," says Charles Morin, a clinical psychologist specializing in insomnia at Laval University in Quebec, Canada. "It carries a very significant burden for the individual — such as increasing the risk of depression and the risk of accidents — and has direct and indirect costs for society, including decreased work productivity."

But treatment options are limited: although insomnia is a long-term condition, sleeping pills are typically recommended for people with significant distress or marked daytime impairment, but only for short-term treatment. One promising alternative is psychotherapy, which includes teaching sleep hygiene, but the sheer number of people experiencing insomnia makes cognitive behavioural therapy impractical as a first-line therapy for the masses.

LITTLE HELPERS

People have been taking substances to induce sleep throughout recorded history. The ancient Egyptians and Greeks used extracts of the opium poppy and the hemp plant[1]. In the second half of the nineteenth century, synthetic drugs such as chloral hydrate and bromide salts, which calm the brain by inhibiting neurons from firing, supplanted these herbal extracts.

Successive waves of sleep-inducing, or hypnotic, drugs have since reached the clinic, each safer and more effective than the last. The first barbiturate — barbitone, or barbital — hit the market in 1904 after its power to send dogs to sleep was discovered. The 1960s brought the benzodiazepines, such as diazepam (Valium) and temazepam. Today's hypnotics of choice, known as 'non-benzodiazepines', reached the clinic in the 1990s, with zolpidem, zopiclone and zaleplon — a group known as the Z-drugs — being most commonly prescribed.

All these hypnotic drugs work in basically the same way: they interact with γ-aminobutyric acid (GABA) receptors in the brain. GABA is the brain's main inhibitory neurotransmitter, calming brain cell activity, which explains why barbiturates and benzodiazepines have also been used as anti-anxiety treatments and

sedatives. In particular, one group of GABA-producing neurons in the hypothalamus forms a key part of the central switch that triggers the change from wake to sleep.

There are two families of GABA receptor: $GABA_A$ and $GABA_B$. Hypnotic drugs bind to the $GABA_A$ receptor, enhancing the action of the GABA neurotransmitter. Because GABA suppresses a multitude of central nervous system functions, enhancing its activity can cause a cascade of side effects. Barbiturates have a notoriously narrow range of safe dosage — taking just a little too much can fatally suppress the brain centres that control heart rate and breathing. Even at lower, non-lethal doses, they can produce amnesia, sometimes causing patients to forget they had taken them and then to take more — a perilous cycle that can easily lead to an overdose[2]. Habitual users can also become physically addicted, experiencing severe withdrawal symptoms when they try to quit the drug.

Benzodiazepines are more potent hypnotics than barbiturates, and are also much less likely to lead to overdose. But some risk of physical or physiological dependence remains, and the drugs are associated with a 'hangover' — a residual drowsiness as the drugs slowly wear off. "A lot of people take sleeping pills because they are afraid their poor sleep is going to impair them the next day," says Daniel Kripke, who studies sleep disorders at the Scripps Clinic in San Diego, California. "But in the vast majority of studies of insomnia, sleeping pills make daytime performance worse, not better."

The Z-drugs have less of a hangover effect than benzodiazepines, thanks to their shorter half-life in the body, so their effects are less likely to be felt the next morning. Comparative studies show that these non-benzodiazepines also generally induce sleep a few minutes faster than benzodiazepines, and they significantly reduce the occurrence of next-day drowsiness[3].

Even Z-drugs can make activities such as driving more dangerous the next morning, however. In one study, more than half of trial participants given zopiclone were worse at driving 8.5 hours later than someone with a blood alcohol content of 0.05%, the legal limit for driving in many countries[4]. A lack of long-term clinical trials and the increased potential for patients to become dependent on sleeping tablets mean that these drugs are still generally recommended only for short-term use[2].

Epidemiological studies suggest there is good reason to be cautious. According to one recent report co-authored by Kripke, patients taking hypnotics such as zolpidem and temazepam were over four times more likely to die during the 2.5-year study period than hypnotic-free control patients[5]. The researchers estimate that sleeping medication played a role in half-a-million deaths in the United States in 2010.

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For more on targeting GABA to influence sleep:
go.nature.com/zLmvyy

HOW SLEEPING PILLS WORK
Several classes of drug share the same mechanism, but others increasingly target different molecular pathways.

Class	Action	Examples
Barbiturates Benzodiazepines Non-benzodiazepines ('Z-drugs')	Increase effect of γ-aminobutyric acid (GABA) by binding to the GABAA receptor (see diagram). The ventrolateral preoptic nucleus (VLPO) in the hypothalamus uses GABA to inhibit wakefulness; more GABA means more sleep	Phenobarbital. Chlordiazepoxide, diazepam, temazepam. Zolpidem, zopiclone, eszopiclone.
Antihistamines	Block histamine in the ascending arousal system	Diphenhydramine, hydroxyzine.
Antidepressants	Inhibit serotonin and histamine receptors	Trazodone, nefazodone.
Adrenergic agonists	Hamper noradrenaline-releasing neurons, block part of the ascending arousal system, and allow the VLPO system to activate	Dexmedetomidine.
Melatonin agonists	Increase the activation of melatonin receptors, a circadian cue that primes the body for sleep via VLPO activation	Melatonin, ramelteon.
Orexin receptor antagonists	Block orexin neurons, inhibiting their wake-promoting signal	Suvorexant, SB-649,868 (both unapproved).

The precise risk of sleeping pills is still not yet known, however. "There is a clear correlation between mortality and the use of hypnotics," says Jian-Sheng Lin, a sleep researcher at Lyon Neuroscience Research Centre in France who is looking for new hypnotic drugs. "However, the causality remains to be demonstrated."

BOUND TO WORK

One route to making sleeping pills safer that looked promising for a while was to make them more selective. $GABA_A$ receptors can be subdivided into several structurally distinct subtypes. Benzodiazepines activate them relatively unselectively, binding to four of the six subtypes (those containing the α1, α2, α3 or α5 subunits). More recent sleeping drugs are less scattershot: zolpidem preferentially binds to receptors containing α1, for example, and another non-benzodiazepine, eszopiclone, has a slight selectivity for those containing α2 and α3.

Researchers are trying to figure out what each subtype does. Genetic neuropharmacologist Uwe Rudolph at McLean Hospital in Belmont, Massachusetts, uses molecular genetics to test whether benzodiazepine's various effects — anxiety relief, sedation and sleep induction — are exerted through specific receptor subtypes. Rudolph's team introduced genetic mutations to disable each subtype in mice, one at a time, and tested benzodiazepine's effects.

When they gave diazepam to mice with a mutated α1 subunit, the drug's sedative properties were lost: it no longer calmed muscle activity when the mice were given a convulsant. When the team mutated the α2 subunit, diazepam lost its anxiety-reducing effects, suggesting that the anti-anxiety effect of the drug operates through this receptor subtype. All the evidence seemed to be falling into place.

The surprises started when Rudolph and colleagues used electroencephalography (EEG) to monitor sleep in mutant mice given diazepam by measuring characteristic shifts in brain activity. "Our prediction was, as α1 is responsible for sedation, then it might be responsible for the sleep-inducing action of diazepam," Rudolph says. "This was not really the case." Instead, mice with a mutated α1 subunit slept just as soundly as wild-type (unmutated) mice when given diazepam.

The EEG readouts of the α2 knockout mouse were just as confusing. This time, there were significant differences between the wild-type mouse and the mutant, suggesting that diazepam's sleep-inducing effects are mediated by receptors containing the α2 subunit[6].

The mixed messages thrown up by the mouse studies have failed to signpost a clear path for improved hypnotic drugs targeting particular $GABA_A$ receptors, says Rudolph. "Part of the problem," he says, "is that existing hypnotics have only weak preferences for GABA subtypes." Drugs with complete subtype selectivity could have clarified the picture — but no such compounds are known, and without stronger evidence that subtype selectivity would improve on today's Z-drugs, drug developers aren't rushing to make them. In the absence of such compounds, the development of new GABA-targeting sleeping pills has stalled.

In the meantime, promising alternative targets have emerged, and the next generation of sleeping pills may sidestep GABA receptors entirely (see 'How sleeping pills work').

One well-travelled path involves histamine blockers, such as doxepin, which has been used for decades as an antidepressant in doses of up to 150 milligrams. "It turns out that lower doses — 3 mg or 6 mg — have some benefit for sleep, and probably very little side effect," Kripke says.

Doxepin generally targets a receptor known as H1, which is found throughout the body. But Lin and his colleagues at Lyon are concentrating instead on the H3 receptor, which is found at high densities in the hypothalamus, where the sleep–wake switch lies[7]. "We use H3-receptor antagonist to treat excessive daytime sleepiness disorders such as narcolepsy, but we think that an H3-receptor agonist could be very useful for insomnia," Lin says. Animal studies

A HISTORY OF SLEEP RESEARCH

The past century has seen a growing research effort to probe – and control – the sleeping brain.

PHILIPPE PLAILLY/SCIENCE PHOTO LIBRARY

1929
Hans Berger records electrical activity of the sleeping brain

1940s
Robert Moore identifies the suprachiasmatic nucleus

1953
Nathaniel Kleitman and Eugene Aserinsky at the University of Chicago, Illinois, describe the rapid eye movement (REM) stage of sleep and propose a correlation with dreaming

1960
Librium, the first benzodiazepine, is launched

1970s
Benzodiazepines begin to replace barbiturates as insomnia treatments

1972
Suprachiasmatic nucleus pinpointed as site of our biologic clock

1977
Frédéric Bremer hypothesizes how the ascending arousal system and VLPO work together as a 'flip flop' switch

1984
Serge Daan proposes that sleep is regulated by circadian and homeostatic processes

1993
US National Institutes of Health (NIH) establishes National Center on Sleep Disorders Research

2001
Louis Ptáček discovers first human gene involved in circadian rhythms

2012
Merck & Co. submits orexin-antagonist suvorexant for US Food and Drug Administration approval

confirm that stimulating the receptor increases sleep. "As a drug target, it is in the proof of concept stage, but we have candidate agonists in development," he adds.

Drug companies also have other targets in their sights. In the late 1990s, several research groups found that narcolepsy can be caused by insufficient amounts of a neurotransmitter called orexin, or by a shortage of orexin-detecting neurons. Since then, several candidate orexin-receptor antagonists have been discovered that mimic the effect of narcolepsy and trigger sleep. Furthest along the development pipeline is suvorexant, for which pharmaceutical company Merck recently filed for approval from the US Food and Drug Administration after it completed clinical trials. The results suggest that suvorexant might be safer than existing sleep medications. Merck recently compared a suvorexant-related compound called DORA-22 with diazepam, zolpidem and eszopiclone in rats and monkeys. DORA-22 was the only drug to promote sleep at doses that did not impair the animals' cognition or memory[8].

MIND OVER MATTER

While drug developers continue to work on a new generation of more effective sleeping pills, Kripke and others think the best solution is already at hand — and has nothing to do with drugs. Cognitive behavioural therapy (CBT) is a form of psychotherapy that aims to remove the dysfunctional thoughts and behaviours that underlie a variety of conditions, from depression to eating disorders.

Learning good sleep hygiene is key to the behavioural component of CBT. Patients must remove from their bedrooms any gadgets and other items that might promote worry or alertness. They are taught to go to bed only when sleepy, and to get out of bed if they find themselves wide-awake for a spell during the night. On the cognitive side, therapists teach relaxation techniques and aim to help patients work through worries that keep them awake. The aim is to break the cycle of being unable to sleep and becoming frustrated.

Numerous studies have found that CBT is a more effective long-term solution for insomnia than sleeping pills. A recent meta-analysis showed that at the end of a course of treatment, benzodiazepines and Z-drugs were approximately as effective as CBT — but that patients taking these drugs who also were given CBT maintained these gains in improved sleep, or even reported further improvements, in the months and years afterwards. No such effects have ever been shown for benzodiazepines or Z-drugs, according to this analysis[9]. Kripke says that compared with hypnotic medication, CBT is "safer, in the long run less expensive, and just plain works better".

But CBT is not a quick fix. A typical six-session course with a therapist is far more time consuming and expensive than simply writing out a prescription for a sleeping pill. "The difficulty with CBT has been getting it out there on a scalable basis," says Colin Espie, a neuroscientist who specializes in sleep research at the University of Oxford, UK. "There are 15 million prescriptions for sleeping pills written annually in the UK, whereas only a few hundred people get access to CBT."

Espie is among a growing group of researchers hoping to make CBT available to the masses by delivering it via the Internet. Alongside online business developer Peter Hames, Espie recently developed a web-based CBT programme called Sleepio. Advice delivered by an animated virtual therapist is tailored to the individual patient — in a section helping patients learn to slow a racing mind, for example, more than two million different response combinations are possible, Espie says. His tests show that web-based CBT is more effective than a placebo — and about as effective as CBT delivered in person by a therapist[10]. The team is investigating how to integrate online CBT with clinical care, for example by developing a portal that allows doctors to monitor their patients' progress. A similar service is already in place in the United Kingdom for web-based CBT to treat depression.

This is a promising start towards helping CBT become a mainstream insomnia treatment, but nobody is arguing that research to develop safer and more effective sleeping pills should stop. It's about being able to offer patients the choice, says Espie — some people will embrace the challenge of working through a CBT programme and making the lifestyle changes needed for long-term benefits, whereas others will simply prefer to pop a pill. Meanwhile, Morin's research shows that CBT and sleeping pills don't have to be mutually exclusive: patients given a short course of zolpidem at the start of their therapy had slightly better long-term improvement than those using CBT alone[11].

So, after countless years of suffering, relief from sleepless nights and daytime sleepiness may soon be within reach, thanks to new drugs being developed and the spread of CBT. Just make sure you leave your smartphone at the bedroom door. ■

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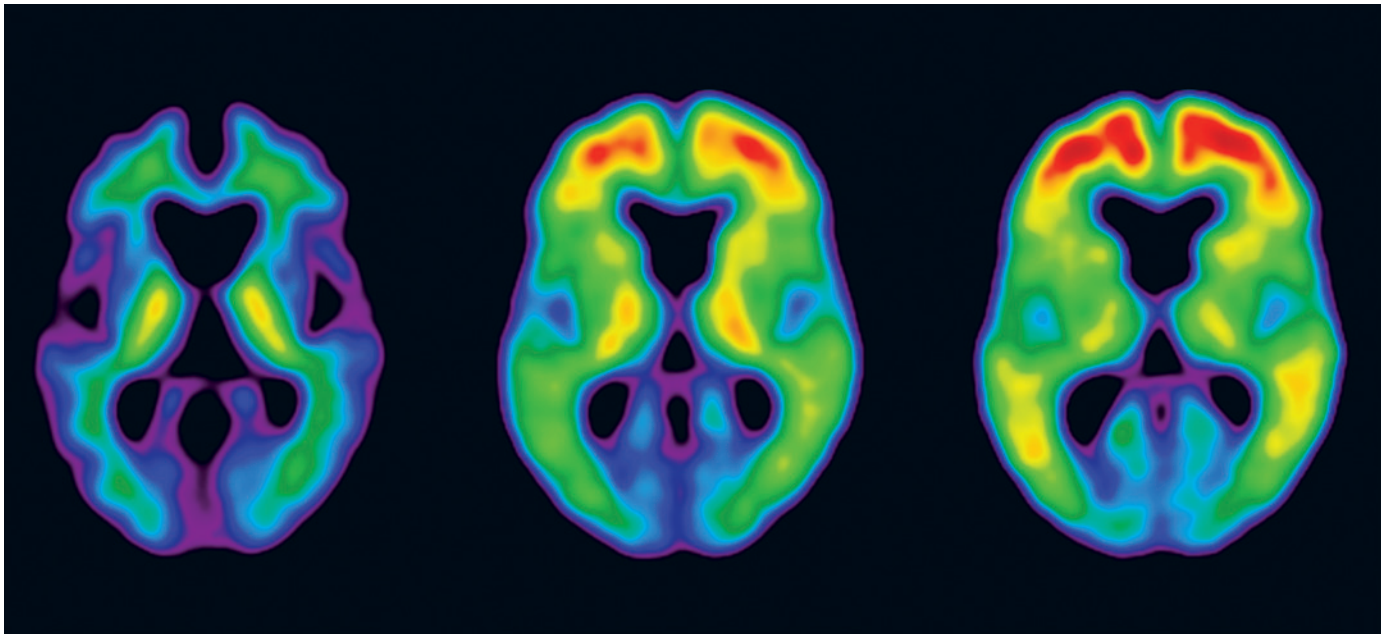

TAMMIE BENZINGER & TYLER BLAZEY, WASHINGTON UNIVERSITY

Patients with preclinical (centre) and clinical (right) Alzheimer's disease show a marked increase in amyloid plaques (red and yellow) in the brain.

NEURODEGENERATION

Amyloid awakenings

Sleep disturbances may be an early sign of neurodegenerative diseases — but could sleep deficits cause these conditions in the first place?

BY MOHEB COSTANDI

Jae-Eun Kang was using a new microdialysis technique to measure how levels of soluble amyloid-β protein in the mouse brain change in response to physiological stress when she noticed something odd. It's thought that the level of soluble amyloid-β correlates with the eventual formation of amyloid-β plaques in the brain, one of the hallmarks of Alzheimer's disease. But Kang found that the protein's concentration seemed to peak during waking hours and fall as the mice slept.

Kang, who was a graduate student in neurologist David Holtzman's lab at Washington University in St Louis, Missouri, at the time, then made a further discovery: depriving the mice of sleep led to a dramatic rise in amyloid-β concentration[1]. "Once we saw that amyloid-β was going up and down with the sleep–wake cycle, the implications began to unfold," says Holtzman. These findings suggested that sleep disturbances might actually precipitate plaque formation. And if a sleep deficit could increase the concentration of soluble amyloid-β, says Holtzman, then sleep abnormalities in earlier life may predispose people to Alzheimer's.

Holtzman's team went on to show that the natural cycle of waking and sleeping breaks down in mice following plaque formation, but is restored again when antibodies are used to eliminate the plaques[2].

This phenomenon is not limited to mice. In people carrying mutations in the presenilin genes, which are strongly linked to the early onset, inherited form of Alzheimer's, Holtzman found that amyloid-β concentration in the cerebrospinal fluid fluctuates to a daily rhythm. He also showed that this cycle breaks down following plaque formation — and before any cognitive symptoms appear[2].

So sleep disturbances might be one of the earliest manifestations of Alzheimer's disease, raising the tantalizing possibility of early intervention to help prevent or slow the inevitable march into the cognitive fog.

EARLY SIGNS

Sleep disturbances might be an early sign of other neurodegenerative conditions as well. Last year, Roxanne Sterniczuk, a neuroscientist at Dalhousie University in Halifax, Canada, looked at data collected from approximately 14,600 people as part of the Survey of Health, Ageing and Retirement in Europe (SHARE), a long-term study of people aged 50 and over across 12 countries.

People who experienced sleep disturbances were more likely to be diagnosed with Alzheimer's within two to four years, according to the SHARE data. In particular, increased daytime sleepiness was the best predictor of the disease. The data also showed that daytime fatigue, a sleep disturbance that leads to exhaustion during the day, predicted those who went on to develop Parkinson's disease.

Parkinson's involves the progressive degeneration of midbrain neurons that produce dopamine — a neurotransmitter involved in regulating the sleep–wake switch. The drugs amphetamine and modafinil, for example, increase wakefulness by increasing dopamine signalling. Conversely, even one night of sleep deprivation reduces the number of dopamine receptors in the striatum, a region of the basal ganglia that is severely affected by the disease. Thus the sleep disturbances associated with Parkinson's may be caused by the degeneration of dopaminergic midbrain neurons.

Sterniczuk plans to analyse the SHARE data again to see if there are subtle differences between the sleep disturbances in presymptomatic Alzheimer's and Parkinson's patients. "If we can characterize the changes before symptoms appear then we can use them as diagnostic markers," she says. "That might permit earlier treatment."

The evidence is building for a correlation between disturbed sleep and neurodegenerative diseases, but the next step — discovering whether sleep disturbances are a cause of these

conditions — will take considerably more research. In particular, establishing a causal relationship will require longitudinal studies that assess the sleeping patterns of large numbers of people over long periods of time, and link specific types of sleep disorder with the incidence of each disease. But to diagnose the diseases accurately, researchers must look for the tell-tale signs in the brains of study participants.

The Memory and Aging Project, run by David Bennett of Rush University Medical Center in Chicago, Illinois, will allow researchers to do that. The study involves 1,200 elderly people who will undergo annual neurological and psychiatric assessments and have agreed to donate their brains for research. Participants wear wrist monitors that record daily patterns of movement, revealing the times they sleep and wake, and their circadian rhythms. "We'll look at circuitry in the hypothalamus that's involved in sleep and circadian rhythms," says Clifford Saper, a neurologist at Harvard Medical School in Boston, Massachusetts, who is collaborating on the project. "Presumably, neurodegenerative diseases disrupt sleep and circadian rhythms by damaging this circuitry."

Testing this hypothesis in humans would be difficult, as it would involve comparing two groups of patients with sleep disorders who are at risk of a neurodegenerative disease, but treating only one group for their sleep problems. "It wouldn't be ethical to withhold treatment from patients, so we'd need to examine how circadian disruption affects neurodegeneration in an Alzheimer's mouse strain," says Saper. "This would take a couple of years, but it may not mimic what happens in humans."

BODY CLOCK

Sterniczuk is doing just that. In her Alzheimer's model, mice usually develop amyloid-β plaques at about 6 months of age and tau tangles — the other hallmark of Alzheimer's — at 12 months. Before then, their patterns of activity for a particular time of day, such as sleeping and feeding, differ from their non-pathogenic counterparts. The Alzheimer's mice also have fewer neurons in the suprachiasmatic nucleus (SCN), the part of the hypothalamus that regulates the circadian rhythm — a deficiency that makes their circadian clocks go off kilter[3].

It's not yet clear whether these changes are associated with altered gene expression in the neurons of the SCN and the raphe nucleus, another part of the brain region that regulates sleep. "I'm trying to find out if changes in the animals' sleep rhythms are associated with altered protein levels in these regulatory regions," Sterniczuk says. If they are, it raises the possibility of gene therapy. "Targeting these genes may alleviate the sleep and circadian-related symptoms, which may in turn slow the progression of cognitive decline."

Fruitflies are also yielding clues to the link between neurodegeneration and circadian rhythms. In 2012, researchers at Oregon State University mutated the *period* gene, which plays a central role in governing the daily circadian rhythm, in fruitflies carrying a mutation in the *sniffer* gene, which causes neurodegeneration. The flies with both mutations degenerated more quickly, and had shorter lifespans, than flies with either mutation alone, suggesting that disrupted circadian rhythms can accelerate the process of neurodegeneration[4].

The findings in mice and flies seem to be directly relevant to humans. In 2005, Jenny Morton, a neurophysiologist at the University of Cambridge, UK, reported that patients with Huntington's disease — a genetic disorder that affects muscle coordination and leads to cognitive decline and psychiatric problems — also have disrupted day–night activity patterns[5]. Moreover, this disturbance is accompanied by marked falls in the expression of two circadian clock genes in a mouse model of the disease.

Expression of the mouse clock gene *mPer2* normally peaks in the morning and dips at night, whereas *mBmal1* follows the opposite pattern, being expressed most at night and least in the morning. But in mice carrying genetic mutations associated with Huntington's disease, the expression profiles of both genes break down. In these mice, *mPer2* expression is lowest in the afternoon, and the rhythmic expression of *mBmal1* ceases altogether. What's more, the expression of both *mPer2* and *mBmal1* is disrupted in the parts of the brain that first succumb to Huntington's disease: the motor cortex and the striatum. These changes in gene expression are probably a result of disrupted circadian rhythms, rather than a cause of it. "We still don't know whether circadian changes are part of these diseases," says Morton. "But if they do turn out to exacerbate the neurodegenerative process, then targeting sleep could be of potential therapeutic benefit."

"A lot of early data suggest that modifying sleep could actually delay the onset of disease."

Genetic variation in clock genes seems to affect people's circadian rhythms, so it may also influence their susceptibility to neurodegeneration. In 2012, for example, Saper's team identified several variations that affect the activity of the human clock gene *PER1* and are associated with being either an early riser or a night owl[6]. "This traces the tendency to be an early riser to a single gene, but we don't know what the implications are for neurodegeneration," he says.

BROKEN DREAMS

Sleeping difficulties and neurodegeneration seem to reinforce one another in a vicious cycle. "Abnormal sleep in mid-life might cause protein aggregation that starts the disease off," Holtzman says, "and the damage that causes may further disrupt sleep."

But could that dynamic be reversed? If disrupted sleep can predispose people to neurodegeneration, then might healthy sleeping patterns help protect the brain against it? Holtzman's group is testing this idea — essentially, whether it is possible to turn the vicious cycle virtuous. "A lot of early data suggest that modifying sleep could actually delay the onset of disease," he says. "I think that's where the field should be going now, but it's not trivial translating all the animal studies directly into people."

Holtzman is not alone in thinking this. Earlier this year, Alpar Lazar, who studies sleep and neurodegenerative disease at the University of Cambridge, presented preliminary data showing that bad sleep can precede the onset of Parkinson's disease by many years. His team found that sleep disturbances — particularly fragmented REM sleep — were more severe in patients who are nearer to disease onset than in those who are further away, who in turn had more disturbed sleep than healthy controls.

Huntington's disease is associated with mutations in the *huntingtin* gene, which contains a short repetitive DNA sequence called a CAG repeat. This repeat sequence is longer in Huntington's patients, leading to the production of misfolded Huntingtin protein. The longer the repeated sequence is, the earlier the disease begins, and the more severe its symptoms. Lazar and colleagues found that longer CAG repeats are also associated with worse sleep disturbances. "Our assumption is that sleep disturbances appear long before disease onset and precipitate disease progression," says Lazar. So, he says, "intervening to improve sleep may slow down the disease process." He is conducting a follow-up study to test this hypothesis.

There is already some evidence for this approach. Sleep apnoea, which is characterised by abnormally shallow and interrupted breathing, may almost double the risk of dementia[7]. Sleep apnoea is treatable, so early intervention could delay the onset not only of neurodegeneration, but also of normal age-related cognitive decline. "Once it is corrected, patients are much brighter and have better memory function," says Saper, "but it's still not clear whether sleep loss itself increases neurodegeneration."

Nevertheless, once clinicians wake up to the fact that sleep is so intimately linked to the most common neurodegenerative diseases, they may be in a better position to detect these debilitating neurological conditions at an early stage, and perhaps stop them in their tracks. ■

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